Mechanisms of Parasitic Pathogenesis
William Petri

The enteric parasites represent a major class of diarrheagenic pathogens for which few effective therapeutic options are available. The World Health Organization estimates that approximately 50 million people worldwide suffer from invasive amebiasis each year, resulting in 40 to 100 thousand deaths. Serologic studies in Mexico demonstrated antibody to *E. histolytica* in 8.4 % of the population. The annual incidence of amebic liver abscess is 21 cases/100,000 inhabitants in Hue City, Vietnam. A prospective study of preschool children in a slum of Dhaka Bangladesh has shown a 9% annual incidence of *E. histolytica* - associated diarrhea or dysentery. In the United States amebiasis is especially a problem in travelers to and in recent immigrants from the developing world, as well as in men who have sex with men. *Entamoeba histolytica* binds intestinal epithelia through a Gal/GalNAc lectin encoded by the *hgl* and *igl* genes. GalNAc-containing neoglycans are potent inhibitors of amebic adherence which may play a role in preventing or reversing colonization at an early stage in the infective cycle. Host cell death soon follow Gal/GalNAc lectin-induced adherence through apoptosis via activation of the host caspase 3 system. Current therapies for asymptomatic infection include iodoquinol, paromomycin, or diloxanide furoate. Invasive amebiasis is presently treated with metronidazole or tinidazole. The degree to which drug resistance in amebiasis has developed is not known at present. Recent advances, including the sequencing of the genome and understanding of molecular pathogenesis, have identified novel drug targets including a family of receptor kinases, cysteine proteinases, alcohol dehydrogenase and Fe-S complex proteins. It would be prudent to invest in the development of new therapies since there is only one class of agents that is currently known to be effective for invasive amebiasis.

Giardia lamblia is the most common parasite identified in stool samples of individuals in the USA, present in ,4% of stool specimens submitted to clinical laboratories. The disease is quite common in developing countries as well, especially in urban slums where a substantial number of children are infected. Water- and food-borne transmission are the most frequent mechanisms of spread, with person to person spread important in day care settings and among sexually active homosexual males. *Giardia lamblia* pathogenesis is similarly poorly defined. Trophozoites of *G. lamblia* can be seen adherent to the intestinal epithelium on small bowel biopsies, and the organism is known to undergo antigenic variation of a family of surface proteins called VSPs. Therapy utilizes metronidazole, tinidazole, or nitazoxanide, with second line agents such as paromomycin, furazolidone or quinacrine sometimes required due to failure of first line therapy.

The spore-forming protozoa (cryptosporidia, cyclospora, isospora, and the microsporidia which are now classified as fungi) are named according to the infectious spore form of the parasite which is spread in a fecal–oral manner. After ingestion of spores from contaminated food or water, sporozoites are released which invade into the intestinal epithelium where they replicate intracellularly. In humans with a normal immune system, infection with an intestinal
spore-forming parasite leads to a self-limited diarrhoea. Treatment is usually not required. CD4 counts at >200 mmm3 are associated with persistent diarrheal infection

with cryptosporidia, isospora, cyclospora and microsporidia. In the USA, C. parvum is the most frequently identified spore-forming parasite in AIDS patients with chronic diarrhoea, whereas in developing countries I. belli and Cyclospora cayetanensis are also frequently identified. *Cryptosporidium parvum* and *C. hominis* can be treated in non-HIV infected with nitazoxanide, but there is no treatment for cryptosporidiosis in the HIV infected. The recent sequencing of the cryptosporidial genome has demonstrated the absence of many metabolic pathways, explaining in part the prior difficulty in developing therapeutics, and at the same time identifying promising therapeutic targets.

The microsporidia include twelve species known to infect humans, the most significant of which are *Enterocytozoon bieneusi* and *E. intestinalis* which can infect through inhalation or oral ingestion of spores. Sporozoites infect epithelial cells of the intestine or respiratory tract. Intestinal *E. bieneusi* is usually treated with fumagillin (not available in the U.S.), and intestinal *Encephalitozoon intestinalis* with albendazole. Symptoms can be ameliorated with octreotide. Disease appears to be confined to the immunosuppressed, although additional studies are needed to delineate its contribution to diarrheal disease in non-immunocompromised individuals. Cyclospora represents a new pathogen in North America. Over 1000 cases have been diagnosed in the US since the summer of 1996. Cyclospora can cause several weeks of diarrhea in immunocompetent patients. In a study among Haitian AIDS patients, 10% of those with diarrhea were chronically infected with Cyclospora. Cyclospora is treated with trimethoprim-sulfamethoxazole or ciprofloxacin. The life-threatening consequences of diarrhea in HIV/AIDS patients necessitate long-term suppression of parasites.

- Research Needs:
    - A better understanding is needed of the metabolic processes and pathways available to parasites
    - The interaction between parasites and host cells (microbial adherence, invasion, and host cell killing) needs to be better characterized
    - Further understanding of diarrheagenic processes are needed
    - Epidemiologic studies to estimate the contributions of the enteric parasites to disease are needed.